PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Naoki TSUCHIYA, et al.

Appln. No.: 10/777,067

Confirmation No.: 5628

Filed: February 13, 2004

For: BENZIMIDAZOLE DERIVATIVE

Docket No: Q79844

Group Art Unit: 1626

Examiner: Laura L. Stockton

SUBMISSION OF EXECUTED DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith is a copy of an executed Declaration Under 37 C.F.R. §1.132 signed by Tsuyoshi MIZUNO, Hidenori KASAI, and Shin UMEDA.

Respectfully submitted,

Susan J. Mack
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WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: September 6, 2006

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DECLARATION UNDER 37 C.F.R. § 1.132

BOX:AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Tsuyoshi MIZUNO, hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received a Master's Degree in 1999 from Kyoto University;

THAT I have been employed by TEIJIN LIMITED, Tokyo, Japan, since April 1999 and by TEIJIN PHARMA LIMITED, Tokyo, Japan, since October 2003; and

THAT I have been engaged in pharmaceutical discovery research as a medicinal chemist in the same companies to date.

I have thorough knowledge of the invention in the above-referenced patent application and I have read the Office Communication dated of March 6, 2006 issued in reference to the

application. In response to the Office Communication, I submit herewith this Declaration comparing 1) the potency of inhibition and 2) Metabolic Rate of 4-Methyl-substituted versus non-substituted Benzothiophene and Indole derivatives and as evidence that the 4-Methyl-substituted derivatives are significantly more potent than the non-substituted derivatives 1) in their ability to inhibit the activity of Chymase and 2) in the Metabolic Rate.

I, Tsuyoshi MIZUNO, am responsible for the synthesis of those compounds for the comparison.

I, Hidenori KASAI, hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received a Master's Degree in 1994 from The University of Tokyo;

THAT I have been employed by TEIJIN LIMITED, Tokyo, Japan, since April 1994 and by TEIJIN PHARMA LIMITED, Tokyo, Japan, since October 2003; and

THAT I have been engaged in pharmacokinetics research, pharmaceutical discovery research and pharmaceutical planning as a biochemist in the same companies to date.

I have thorough knowledge of the invention in the above-referenced patent application and I have read the Office Communication dated of March 6, 2006 issued in reference to the application. In response to the Office Communication, I submit herewith this Declaration comparing 1) the potency of inhibition and 2) Metabolic Rate of 4-Methyl-substituted versus non-substituted Benzothiophene and Indole derivatives and as evidence that the 4-Methyl-

substituted derivatives are significantly more potent than the non-substituted 1)in their ability to inhibit the activity of Chymase and 2) in the Metabolic Rate.

I, Hidenori KASAI, am responsible for the assay of Chymase inhibitory activity for the comparison.

I, Shin UMEDA, hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received a Doctor's Degree in 2005 from Chiba University;

THAT I have been employed by TEIJIN LIMITED, Tokyo, Japan, since April 1991 and by TEIJIN PHARMA LIMITED, Tokyo, Japan, since October 2003; and

THAT I have been engaged in Pharmacokinetics Research as a biochemist in the same companies to date.

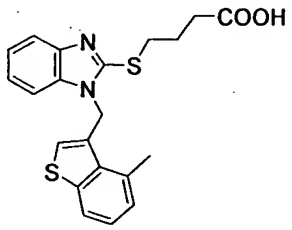
I have thorough knowledge of the invention in the above-referenced patent application and I have read the Office Communication dated of March 6, 2006 issued in reference to the application. In response to the Office Communication, I submit herewith this Declaration comparing 1) the potency of inhibition and 2) Metabolic Rate of 4-Methyl-substituted versus non-substituted Benzothiophene and Indole derivatives and as evidence that the 4-Methyl-substituted derivatives are significantly more potent than the non-substituted 1) in their ability to inhibit the activity of Chymase and 2) in the Metabolic Rate.

I, Shin UMEDA, am responsible for the Metabolic Rate of our compounds for the comparison.

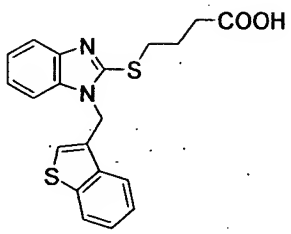
Comparison of 1) the potency of inhibition and 2) Metabolic Rate of 4-Methyl-substituted versus non-substituted Benzothiophene and Indole derivatives for inhibitor of Chymase

Selection of compounds to be compared

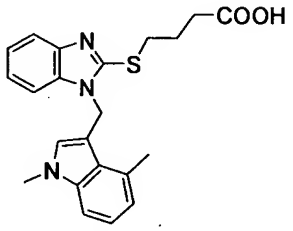
I selected 4 Compounds in Figure.1 below.



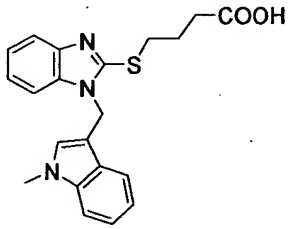
Compound A
Compound 58 in the Appln. No.: 10/777,067



Compound B
Compound 459 in the Appln. No.: 10/963,710
Compound 52 in the Appln. No.: 10/777,067



Compound C
Compound 39 in the Appln. No.: 10/777,067



Compound D
Compound 460 in the Appln. No.: 10/963,710
Compound 34 in the Appln. No.: !0/777,067

Figure.1

Compound A (it is equal to the compound 58 in the application No.10/777,067.) has a 4-methyl-substituted Benzothiophene, and Compound B (it is equal to the compound 459 in the application No.10/963,710, and the compound 52 in the application No.10/777,067.) has no substituent at 4 position on the Benzothiophene.

Compound C (it is equal to the compound 39 in the application No.10/777,067.) has a 4-methyl-substituted Indole, and Compound D (it is equal to the compound 460 in the application No.10/963,710, and the compound 34 in the application No.10/777,067.) has no substituent at 4 position on the Indole.

There is only a single difference in these two sets of compounds; that is whether or not each compound has a substituent (Methyl) on the 4 position of Benzothiophene or Indole.

Materials and methods

Synthetic routes of Compound A and Compound C are the same as Example 2 in the application No. 10/777,067. Synthetic routes of Compound B are the same as Example 2 in the application No. 10/963,710 and Compound D are the same as Example 10 in the application No. 10/963,710.

Enzyme Assay

The Human Mast Cell Chymase was prepared in the same way as Example 16 in the application No. 10/777,067 or Example 22 in the application No. 10/963,710 and our compounds

are assayed in the same way as Example 17 in the application No. 10/777,067 or Example 23 in the application No. 10/963,710. The concentration of the specimen at 50 % inhibition activity was determined as the indication of Chymase inhibiting activity (IC_{50}).

Metabolic Rate Measurement

Metabolic Rate (MR) was measured in the same way as Example 20 in the application No. 10/777,067. Compound B (Compound 459 in the application No.10/963,710.) is equal to Compound 52 in the application No. 10/777,067. And Compound D (Compound 460 in the application No. 10/963,710) is equal to Compound 34 in the application No. 10/777,067.

The results including Chymase inhibiting activity and Metabolic Rate are shown in Table 1.

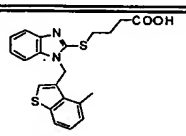
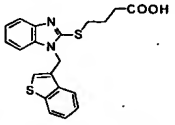
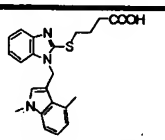
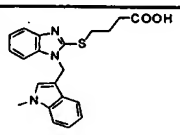
	Compound No. in application No.10/777,067	Compound No. in application No.10/963,710	substituent at 4 position of Benzothiophene or Indole	structure	IC50(nM) value range in our applications	IC50(nM) actual value	MR
Benzothiophene Deriva	58		Me		1-10	2.85	0.048
	52	459	non		10-100	22.1	0.331
Indole Derivatives	39		Me		1-10	4.75	0
	34	460	non		10-100	90.3	0.26

Table 1

Conclusions

From the data in Table 1, it can be seen that 4-Substituted(Methyl)-Benzothiophene and Indole derivatives, Compound A and Compound C, are unexpectedly more potent in Chymase inhibitory activity and have unecpectedly lower Metabolic Rate than non-substituted ones, Compound B and Compound D.

We declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Aug. 23, 2006

水野剛之
Tsuyoshi MIZUNO

Date: Aug. 25, 2006

笠井秀寛
Hidenori KASAI

Date: AUG. 23, 2006

梅田晋
Shin UMEDA